

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

IN THE CLAIMS

This listing of claims replaces all prior listings of claims in this application.

1. (currently amended) A process for preparing ~~a mixture of a bis (5, 7, 3', 4'-tetra-O-protected) epicatechin (4 β ,8)₂-trimer and other oligomers~~ a tris (5, 7, 3', 4'-tetra-O-protected) epicatechin (4 β ,8)₂-trimer comprises the step of coupling a 5,7,3',4'-tetra-O-protected epicatechin monomer with a 5,7,3',4'-tetra-O-protected-4-acyloxy-epicatechin monomer in the presence of an acidic clay.
2. (currently amended) A process for preparing a mixture of ~~of 5, 7, 3', 4'-tetra-O-protected epicatechin (4 β , 8)-oligomers~~ tris (5, 7, 3', 4'-tetra-O-protected) epicatechin (4 β , 8)₂-trimer and tetrakis (5, 7, 3', 4'-tetra-O-protected) epicatechin (4 β , 8)₃-tetramer comprises the step of coupling a bis (5, 7, 3', 4'-tetra-O-protected) epicatechin (4 β , 8)-dimer with a 5,7,3',4'-tetra-O-protected-4-acyloxy epicatechin monomer in the presence of an acidic clay.
3. (currently amended) The process of Claim 1 or 2, wherein the acidic clay is a ~~mormorillonite~~ Montmorillonite clay.
4. (currently amended) The process of Claim 1, wherein the protecting groups ~~on the protected monomers~~ are protecting groups which do not deactivate the A ring of the protected monomers.
5. (currently amended) The process of Claim 2, wherein the protecting groups on the protected ~~oligomer~~ dimer are protecting groups that do not deactivate the A ring of the upper mer of the ~~oligomer~~ dimer and the protecting groups on the protected monomer are protecting groups that do not deactivate ~~that the~~ the A ring of the monomer.

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

6. (currently amended) The process of Claim 4 or 5, wherein the protecting groups are benzyl groups.
7. (currently amended) The process of Claim 1 or 2, wherein the 4-acyloxy group is a C₂-C₆ alkoxy group having a terminal ~~hydroxyl~~ hydroxy group.
8. (currently amended) The process of Claim 7, wherein the C₂-C₆ alkoxy group having the terminal ~~hydroxyl~~ hydroxy group is a 2-hydroxyethoxy group.
9. (originally presented) The process of Claim 1, wherein the protected monomers are 5,7,3',4'-tetra-*O*-benzyl-epicatechin and 5,7,3',4'-tetra-*O*-benzyl-4-[2-hydroxyethoxy]-epicatechin; wherein the mixture comprises the benzyl-protected epicatechin (4 β , 8)-dimer and benzyl-protected epicatechin (4 β , 8)₂ trimer.
10. (currently amended) The process of Claim 9, wherein the ~~benzyl-protected 5, 7, 3', 4'-tetra-*O*-benzyl-epicatechin-(4 β ,8)-dimer~~ is the major product in the mixture.
11. (currently amended) The process of Claim 2, wherein the ~~oligomer is a benzyl-protected (4 β , 8)-dimer~~ dimer is bis (5, 7, 3', 4'-tetra-*O*-benzyl) epicatechin (4 β ,8)-dimer; and wherein the monomer is 5,7,3',4'-tetra-*O*-benzyl-4-[2-hydroxyethoxy] epicatechin; and wherein the mixture comprises ~~a benzyl-protected epicatechin (4 β , 8)-dimer, a [(4 β , 8)]₂-benzyl-protected epicatechin trimer, and a benzyl-protected epicatechin (4 β , 8)₃-tetramer~~ bis (5, 7, 3', 4'-tetra-*O*-benzyl) epicatechin (4 β ,8)-dimer, tris (5, 7, 3', 4'-tetra-*O*-benzyl) epicatechin (4 β ,8)₂-trimer, and tetrakis (5, 7, 3', 4'-tetra-*O*-benzyl) epicatechin (4 β ,8)₃-tetramer.

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

12. (currently amended) The process of Claim 1, further comprising the step of separating the protected monomer(s), protected dimer, and other and/or protected oligomers trimer from the monomer by column chromatography.

13. (currently amended) The process of Claim 2, further comprising the step of separating the protected oligomers and protected monomer monomer(s), protected dimer, protected trimer, and protected tetramer by column chromatography.

14. (currently amended) The process of Claim 12 or 13, further comprising the step of replacing the protecting groups on the separated ~~dimers~~ dimer, and/or oligomers trimer, and/or tetramer with hydrogen.

15. (currently amended) A process for preparing a mixture of benzyl-protected (4 β , 8)-oligomers of epicatechin or catechin comprises reacting a 5, 7, 3', 4'-tetra-*O*-benzyl-protected-epicatechin or -catechin monomer or a 5, 7, 3', 4'-tetra-*O*-benzyl-protected-(4 β ,8)-epicatechin ~~or catechin or catechin~~ oligomer and with 3-*O*-acetyl-4-[(2-benzothiazolyl)thio]-5, 7, 3', 4'-tetra-*O*-benzyl-epicatechin in the presence of silver tetrafluoroborate.

16. (currently amended) A process for preparing a mixture of acetyl-protected and benzyl-protected (4 β ,8)-oligomers of epicatechin or catechin comprises reacting a 3-*O*-acetyl-5,7,3',4'-tetra-*O*-benzylepicatechin monomer or a 3-*O*-acetyl-5,7,3',4'-tetra-*O*-benzylepicatechin (4 β ,8)-oligomer and 3-*O*-acetyl-4-[(2-benzothiazolyl)thio]-5,7,3',4'-tetra-*O*-benzylepicatechin in the presence of silver tetrafluoroborate. ~~a 3-*O*-acetyl-5,7,3',4'-tetra-*O*-benzylepicatechin monomer or a 3-*O*-acetyl-5,7,3',4'-tetra-*O*-benzylepicatechin (4 β ,8)-oligomer and with~~ 3-*O*-acetyl-4-[(2-benzothiazolyl)thio]-5,7,3',4'-tetra-*O*-benzyl-epicatechin in the presence of silver tetrafluoroborate.

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

17. (amended) The process of Claim 15 or 16, wherein oligomers are 5, 7, 3', 4'-tetra-O-benzyl-protected (4 β ,8) epicatechin-oligomers, and wherein the silver tetrafluoroborate is dried before the reaction.
18. (originally presented) The process of Claim 17, wherein the drying is vacuum drying carried out immediately before the reaction.
19. (amended) The process of Claim 16, wherein the mixture comprises protected ~~trimer trimers~~ through protected ~~octamers~~. heptamer when the protected oligomer is the dimer, protected tetramer through the protected octamer when the protected oligomer is the trimer, and the protected pentamer through the protected undecamer when the protected oligomer is the tetramer.
20. (amended) The process of ~~Claim 15 or~~ 16, further comprising the step of isolating the protected oligomers in the mixture by reverse phase high pressure liquid chromatography.
21. (originally presented) The process of Claim 20, further comprising the step of removing the acetyl-protecting group(s) from the isolated oligomers.
22. (currently amended) The process of Claim 21, wherein the acetyl-protecting group(s) ~~removal is carried out~~ are removed with aqueous tetra-n-butyl ammonium hydroxide.
23. (originally presented) The process of Claim 20, further comprising the step of removing the benzyl-protecting groups from the isolated oligomers.

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

24. (currently amended) The process of Claim 23, wherein the benzyl-protecting groups ~~removal is carried out~~ are removed by hydrogenolysis.

25. (currently amended) The process of Claim 20, further comprising the steps of removing the acetyl protecting ~~group(s)~~ groups and then removing the benzyl protecting groups ~~from the isolated oligomers~~.

26. (currently amended) The process of Claim 25, wherein the acetyl protecting group(s) ~~removal is carried out~~ are removed with aqueous tetra-n-butyl ammonium hydroxide and wherein the benzyl-protecting groups ~~removal is carried out~~ are removed by hydrogenolysis.

27. (currently amended) A process for preparing a mixture of 5,7,3',4'-tetra-*O*-benzyl-epicatechin-(4 β ,8)-oligomers comprises the steps of:

(a) activating with 2-(benzothiazolyl)thio groups the C-4 positions of each of epicatechin the C-4 position of 5,7,3',4'-tetra-*O*-benzyl-epicatechin with a 2-(benzothiazolyl)thio group to form 4-[(2-benzothiazolyl)thio]-5, 7, 3', 4'-tetra-*O*-benzylepicatechin; and

(b) self-condensing the ~~activated, protected monomers~~ the 4-[(2-benothiazolyl)thio]-5,7,3',4'-tetra-*O*-benzylepicatechin in the presence of silver tetrafluoroborate or an acidic clay ~~to form a benzyl-protected condensed epicatechin (4 β ,8) oligomer~~ the mixture of 5,7,3',4' tetra-*O*-benzylepicatechin (4 β ,8) oligomers.

28. (currently amended) The process of Claim 27, further comprising the steps of separating the protected dimer, trimer, and tetramer oligomers and removing the benzyl protecting groups.

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

29. (currently amended) A process for chain extending a protected epicatechin (4 β ,8) oligomers oligomer with a C-4 activated, protected epicatechin (4 β ,8) oligomer comprises the step of condensing an epicatechin (4 β ,8)-oligomer having 3-O-acetyl-acetyl protecting groups at the 3-positions of all mers, ~~and~~ 5,7,3',4'-tetra-O-benzyl protecting groups ~~on~~ at the 5, 7, 3' and 4' positions of all mers, and having a ~~C-4-[2(benzothiazolyl)thio]~~ C-4-[2-(benzothiazolyl)thio] activating group on a terminal mer with an epicatechin oligomer having ~~3-O-acetyl~~-acetyl protecting groups at the 3-positions of each mer and 5,7,3',4'-tetra-O-benzyl benzyl protecting groups at the 5, 7, 3' and 4' positions ~~on~~ of each mer in the presence of silver tetrafluoroborate or an acidic clay.

30. (~~originally presented~~currently amended) The process of Claim 29, wherein one of the C-4 activated, protected oligomers is ~~a 3-O-acetyl-5,7,3',4'-tetra-O-benzyl~~epicatechin (4 β ,8) [~~3-O-acetyl-4-[(2-benzothiazolyl)thio]-5,7,3',4'-tetra-O-benzyl~~epicatechin]3-O-acetyl-5,7,3',4'-tetra-O-benzyl-epicatechin-(4 β ,8)-3-O-acetyl-4-[(2-benzothiazolyl)thio]-5,7,3',4'-tetra-O-benzyl-epicatechin; wherein the benzyl-protected oligomer is tetrakis (3-O-acetyl-5,7,3',4'-tetra-O-benzyl)epicatechin (4 β ,8)₃-tetramer~~tetrakis (3-O-acetyl-5,7,3',4'-tetra-O-benzyl)epicatechin (4 β ,8)₃-tetramer~~[.,.]; wherein the protected, chain-extended oligomer is hexakis (3-O-acetyl-5,7,3',4'-tetra-O-benzyl-tetramer-epicatechin) (4 β ,8)₅-hexamer~~hexakis (3-O-acetyl-5,7,3',4'-tetra-O-benzyl)epicatechin (4 β ,8)₅-hexamer~~.

31. (originally presented) ~~4-[(2-Benothiazolyl)thio]-5,7,3',4'-tetra-O-benzyl~~epicatechin~~4-[(2-Benothiazolyl)thio]-5,7,3',4'-tetra-O-benzyl-epicatechin~~ or 4-[(2-benzothiazolyl)thio]-5,7,3',4'-tetra-O-benzyl-epicatechin 4-[(2-benzothiazolyl)thio]-5,7,3',4'-tetra-O-benzyl-catechin.

32. (currently amended) A process for preparing the ~~compound~~ 4-[(2-benzothiazolyl)thio]-5,7,3',4'-tetra-O-benzyl-epicatechin of Claim 31 comprises reacting 5,7,3',4'-tetra-O-benzyl-4-(2-hydroxyethoxy)-

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

epicatechin or ~~5,7,3',4'-tetra-O-benzyl-4-(2-hydroxyethoxy)catechin~~ with an organoaluminum thiolate generated from 2-mercaptobenzothiazole.

33. (originally presented) 4-[(2-Benzothiazolyl)thio]-3-O-acetyl-5,7,3',4'-tetra-O-benzyl-epicatechin or 4-[(2-benzothiazolyl)thio]-3-O-acetyl-5,7,3',4'-tetra-O-benzyl-catechin.

34. (currently amended) A process for preparing the compound 4-[(2-benzothiazolyl)thio]-3-O-acetyl-5,7,3',4'-tetra-O-benzyl-epicatechin of Claim 33 comprises reacting 5,7,3',4'-tetra-O-benzyl-4-(2-hydroxyethoxy)-epicatechin or ~~5,7,3',4'-tetra-O-benzyl-4-(2-hydroxyethoxy)catechin~~ with an organoaluminum thiolate generated from 2-mercaptobenzothiazole followed by acetylation.

35. (currently amended) A process for preparing a (4 β ,8)-dimer comprises the step of reacting ~~4-(benzylthio)-catechin~~ 4-(benzylthio) epicatechin or 4-(benzylthio)catechin with epicatechin or catechin in the presence of silver tetrafluoroborate or dimethyl (methylthio) sulfonium tetrafluoroborate.

36. (originally presented) ~~4-(Benzylthio)epicatechin~~ 4-(Benzylthio)epicatechin or 4-(benzylthio)catechin.

37. (originally presented) A process for preparing the compound of Claim 36 comprises reacting epicatechin or catechin with benzyl mercaption.

38. (originally presented) A method of treating breast cancer in a mammal in need of such treatment, which treatment inhibits cancer cell growth through cell cycle arrest in the Go/G phase and comprises

Applicant: Kozikowski et al.
Serial No.: 10/658,241
5677-177

administering to the mammal epicatechin-(4 β ,8)₄-pentamer, wherein the breast cancer cells are selected from the group consisting of human breast cancer cell lines MCF-7, SKBR-3, MDA 435, and MDA MB-231.

39. (originally presented) The method of Claim 38, wherein the pentamer is a purified procyanidin fraction isolated from cocoa beans as a cocoa extract.

40. (originally presented) The method of Claim 39, wherein the pentamer is a synthetically prepared procyanidin.

41. (originally presented) The method of Claim 39, wherein the breast cancer cells are from the MDA MB-231 cell line.